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DRUG DISCOVERY

A comparative evaluation of the sustained release properties of *Sus scrofa domesticus* fat and carnauba wax in ibuprofen matrix granule formulations

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ABSTRACT

The study investigated the sustain drug release ability of *Sus scrofa domesticus* (SSD) fat in comparison with carnauba wax in ibuprofen matrix granule formulations. SSD fat was extracted by wet rendering and used to prepare ibuprofen granules at varying concentrations of the fat and carnauba wax (2.5-10%w/w) and maize starch mucilage (15%w/w). Granules were evaluated for micromeritic parameters and drug-excipient interaction using Differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy. The granules were packed in hard gelatin capsules and their *in vitro* drug release and release kinetics evaluated. SSD fat granules exhibited poor flow properties with angles of repose ≤ 40.40° and Carr's indices≤38%while those of carnauba wax were free flowing with angles of repose ≤ 31°Cand Carr's indices ≤ 19%. DSC and FTIR analyses showed no interaction between the fat and ibuprofen. Drug release from the granules decreased with increase in fat and wax concentrations. Granules formulated with 5.0-10%w/w of the SSD fat exhibited superior drug retardation within 4 h with percentage release of 43, 37 and 27%, respectively, as against the 50% release of granules with 10%w/w of carnauba wax. Drug release from the SSD fat granules fitted with the Korsmeyer-Peppas model, indicating a Super Case-II diffusion mediated drug release mechanism. The drug release profiles of ibuprofen granules formulated with SSD fat showed significant drug release retardation and were superior to those prepared with carnauba wax at test concentrations. Hence the SSD fat will find potential application as a matrix former in sustained or controlled release preparations.

Keywords: *Sus scrofa domesticus*, ibuprofen, granules, sustained release

1. INTRODUCTION

Oral dosage forms are one of the most convenient drug delivery system available till date with about 50 % of available drugs in the market formulated as tablets for oral administration (Shivakumar *et al*., 2004, Sharma *et al*., 2009, Patilet *al*., 2016). These tablets range from the sublingual or oral disintegrating tablets (ODT) or fast disintegrating tablets (FDT) to the enteric coated tablets that are meant to withstand the acidic environment of the stomach and reach the small intestine (Shargel *et al*., 2012).

These oral dosage formulations have also advanced with time from the simple immediate release tablets to more complex forms such as the modified or sustained release tablets. Modified drug release is achieved with the use of various polymers which are either synthetic or natural, employed as a matrix coating material to enclose drug particles and hinder their release. Matrix forming polymers includes hydrogels e.g. acrylate polymethacrylates, soluble polymer e.g. polyethylene glycols, biodegradable and non-biodegradable polymers, mucoadhesive polymers and natural gum and waxes (Dash and Varma, 2013).

Most pharmaceutical raw materials are imported in Nigeria with foreign currency and this has accounted for the high foreign exchange expenditure in manufacturing and the overall consequences is that the final product is too expensive and unaffordable. Nigeria as a nation is endowed with biodiversity of natural resources as raw materials which can be tapped and utilise for the economic growth and development of indigenous pharmaceutical industry.

With the increasing interest in pharmaceutical grade raw materials locally obtainable from animal and plants sources because of their availability, affordability and environmentally friendly nature (Ogaji *et al*., 2012), natural fats are being investigated as substitutes for the synthetic matrix forming polymers (Umekoli *et al*., 2009, Attama *et al*., 2009, Eichie *et al*., 2010, Momoh *et al*., 2013). Fats, refined and purified to pharmaceutical grade have found wide ranging applications as binders, fillers, solubilizers, lubricants, emollients and emulsifiers in several dosage forms such as tablets, capsules, emulsions, suppositories and semi-solid cosmetic preparations (Grassa, 2000).

Sus scrofa domesticus fat is obtained from the adipose tissues of the domestic specie of the wide pig family (Suidae), genus (Sus) and specie (*Sus scrofa*). It is usually considered a waste product after taking away the fleshy meat of the pig. The fat is used in place of butter for cooking or shortening in several western delicacies (Alfred, 2002, Ockerman and Basu, 2006). This study sets out to investigate the pharmaceutical usefulness of *Sus scrofa domesticus* fat as a drug release retardant in the preparation of ibuprofen granule formulations.

Ibuprofen is classified as a non-steroidal anti-inflammatory drug (NSAID) commonly used in treating conditions such as rheumatoid or osteo-arthritis. It is given at a dose of 200 - 400 mg orally every 4-6 hours daily because of its short half-life of 1.8 - 2.0 hours (Goodman and Gilman, 2001, Juhari *et al*., 2009). This dosing frequency makes ibuprofen a model drug candidate requiring sustained or extended release formulation.

2. MATERIALS AND METHODS

Materials

Ibuprofen (Emzor Pharmaceutical Ltd, Lagos, Nigeria), carnauba wax (Halewood Chemicals Ltd, England). *Sus scrofa domesticus* fat was extracted from the adipose tissues of various parts of the domestic pig obtained from an abattoir in Benin City, Edo State, Nigeria.

Methods

The extraction, purification and physicochemical characterization of *Sus scrofa domesticus* fat have been previously reported (Uzochukwu *et al*., 2020).

Preparation of ibuprofen granules

The formula employed in preparing different batches of granules are shown in Table 1. Using melt granulation, the required amounts of ibuprofen powder and the molten SSD fat or carnauba wax was triturated in a mortar with a pestle into a homogeneous masse. The mass was double screened by using a 1.7 mm sieve and then a700 µm sieve and the resulting granules air dried. While the conventional granules were prepared using wet granulation method by mixing the required amount of ibuprofen powder with sufficient amounts of maize starch mucilage into a wet mass. The wet mass was screened using a 1.7 mm sieve and the wet granules obtained were dried in a hot air oven at 60 °C for 30 min. The granules were further passed through a 700 µm sieve and dried for another 1.0 h at the same temperature. Resulting granules from both methods were stored in airtight containers in a desiccator with activated silica gel before their evaluations.

Table 1: Formula for the preparation of ibuprofen granules

Ingredients (mg)	Batches								
	SD1	SD2	SD3	SD4	CW1	CW2	CW3	CW4	CG
Ibuprofen	200	200	200	200	200	200	200	200	200
SSD fat	5	10	15	20	-	-	-	-	-
Carnauba wax	-	-	-	-	5	10	15	20	-
Maize starch mucilage (15 %w/w)	-	-	-	-	-	-	-	-	qs

Evaluation of granules

The formulated granules were evaluated to the following micromeritic characterizations;

Bulk and tapped densities

About 5.0 g of granules was poured into a measuring cylinder and the volume occupied was noted. The cylinder was subjected to 100 taps on a wooden platform and the tapped volume noted. The ratio of the granule weight to their respective volumes was recorded as the bulk and tapped densities (Carr, 1965).

Hausner's ratio

The ratio was determined by dividing the tapped density with the bulk density of the granules (Carr, 1965).

Carr's index

The difference between the tapped and bulk densities was divided by the tapped density and result expressed as percentage (Carr, 1965).

Angle of repose

Using the method of Richards (1972a), 5.0 g weight of granules was poured down a funnel clamped with a retort stand and 3 cm above a white sheet of paper on a platform. The radius or mean diameter of the base of the cone heap formed by the granules was determined and the angle of repose calculated using Equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots\ldots \quad (1)$$

Where θ = angle of repose, h = height of the heap of granules and r = radius of the base of the heap of granules.

Flow rate

Using the method of Carstensen and Chan (1977), a clean sheet of paper was placed directly at the base of a clamped funnel. With the funnel outlet closed, 5.0 g of granules was introduced into the funnel. The outlet was opened and the granules allowed to fall freely under gravity. The flow rate was calculated as a ratio of the weight of granules to the time taken for the funnel to completely empty the granules.

Entrapment efficiency

Using the method of Eichie *et al*. (2010), 1.0 g of ibuprofen granules was soaked in 500 ml of phosphate buffer pH 7.2 at 40 °C for 24 h and stirred intermittently. The solution was cooled to 0 °C and the frozen fat or wax mass was decanted and the supernatant's ibuprofen content analysed spectrophotometrically at 221 nm (T70, PG Instruments Ltd, USA). While for the maize starch mucilage granules, an aliquot was taken from the 24 h solution and filtered before analysis. The entrapment efficiency was calculated using Equation 2.

$$Entrapment\ efficiency(\%) = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100 \quad \ldots\ldots\ldots \quad (2)$$

Differential scanning calorimetry (DSC)

Using a Mettler Toledo DSC821e Differential Scanning Calorimeter (Switzerland), an aluminium pan containing 5.0 mg portion of the sample was sealed. The seal was pieced to allow dehydration of samples. The pan was placed in the equipment holder and heated from 60 - 300 °C at a heating rate of 10 °C/min and flushing with 80 ml of N_2/min. Melting peaks, transition temperatures and enthalpies were measured and calculated using the Mettler star software. This procedure was carried out for ibuprofen powder and the batch of granules containing 10.0 %w/w (SD4) of SSD fat.

Fourier transform infrared spectroscopy (FTIR)

The potassium bromide (KBr) pellet method was used. Five milligrams (5.0) portion of the samples were mix with potassium bromide powder and compressed into a disk using a press. The disk was scanned in a spectrophotometer (Shimadzu FTIR 8400S) over the range of 500-4500cm^{-1}. Absorption bands on the spectra of the ibuprofen powder and the batch of granules containing 10.0 %w/w (SD4) of SSD fat was studied for evidence of interactions.

Filling of granules into gelatine capsules

Since attempts in compressing the granules into hard compact tablets failed by producing crumbling tablets, 200 mg weight of granules were filled into 250 mg capacity hard gelatin capsules in readiness for drug release studies.

***In vitro* drug release studies**

the BP paddle method was used for the dissolution tests. A dissolution test apparatus holding 900 ml of phosphate buffer solution of pH 7.2, maintained at 37 ± 0.5 °C with a revolution speed of 50 rpm was used (Caleva ST7, UK). Three (3) capsules were selected at random from the different batches and used for the test. At predetermined intervals, 5.0 ml samples were withdrawn from the dissolution or leaching fluid for 4 h. The withdrawn sample was replenished with an equivalent volume of fluid of same temperature (37 ± 0.5 ºC). The withdrawn samples were filtered and diluted twice with phosphate buffer solution. The absorbances of the resulting solutions were measured at λmax 221 nm, using a spectrophotometer (T70, PG Instruments Ltd, USA). The percentage of drug released was then calculated using the equation from the standard calibration plot obtained from the pure ibuprofen.

***In vitro* release kinetics**

Data from the *in vitro* drug release studies were fitted into different kinetic model equations to determine the mode and mechanism of ibuprofen release from the granules. The kinetic models used were:

Q = kt (zero-order) (Richards, 1972b) ..... (3)
In (1-Q) = -kt(first-order)(Wagner, 1969) ..... (4)

$Q = kt^{1/2}$ **(**Higuchi) (Higuchi, 1968) . ..... (5)

Log Q = log k + n log t (Korsemeyer-Peppas) (Korsemeyer *et al.*, 1983) ..... (6)

Where, Q is the fraction of ibuprofen released at time t, k is the release rate constant and n is the diffusional exponent.

Statistical analysis

Data was subjected to descriptive statistics using Microsoft Excel (2013). Means and standard deviations were calculated and the difference between mean was determined at 95 % confidence interval with ANOVA.

3. RESULTS

Granule properties

The results from the evaluations of the ibuprofen granules prepared with *Sus scrofa domesticus* fat and carnauba wax are presented in Tables 2a and b. The bulk and tapped densities of the granules were between 0.30 - 0.49 and 0.52 - 0.59 g/cm^3, respectively. The Hausner's ratios and Carr's indices of the granules ranged from 1.11 - 1.61 and 10.90 -36.20 %, respectively, indicating 'excellent' to 'poor' flow properties. The angles of repose values of the granules were between 14.50 - 40.00° while their flow rates values ranged from 1.40 - 0.15 g/s, respectively. Generally, the conventional granules exhibited excellent flow properties while the SSD fat and carnauba wax granules decreased in their flowability with increase in the amounts of the fat or wax with the wax granules superior at all test concentrations. Granule batches prepared with the fat had an average drug entrapment efficiency of 25.0 % as against 70.0 % of carnauba wax granules.

Table 2a: Some physical properties of ibuprofen granules formulated with SSD fat

Batches	**SD1**	**SD2**	**SD3**	**SD4**	**CG**
Fat Conc. (% w/w)	**2.5**	**5**	**7.5**	**10**	**15**
Bulk density (g/cm^3)	0.41 ± 0.02	0.40 ± 0.01	0.41 ± 0.03	0.34 ± 0.02	0.30 ± 0.02
Tapped density (g/cm^3)	0.58 ± 0.30	0.58 ± 0.03	0.58 ± 0.04	0.55 ± 0.03	0.52 ± 0.03
Hausner's ratio	1.41 ± 0.12	1.45 ± 0.12	1.41 ± 0.12	1.61 ±0.12	1.11 ± 0.05
Carr index (%)	29.3 ± 0.02	31.0 ± 0.02	29.0 ± 0.02	38.0 ± 0.02	36.2 ± 1.20
Angle of repose (°)	36.3 ± 1.31	39.0 ± 1.00	40.4 ± 1.25	40.0 ± 2.10	14.5 ± 0.12
Flow rate (g/sec)	0.50 ± 0.02	0.35 ± 0.02	0.26 ± 0.02	0.15 ± 0.02	1.43 ± 0.05
Entrapment efficiency (%)	25.0 ± 0.10	25.0 ± 0.11	24.6 ± 0.12	24.4 ± 0.22	99.0 ± 0.02

± Standard Deviation

Table 2b: Some physical properties of ibuprofen granules formulated with carnauba wax

Batches	**CW1**	**CW2**	**CW3**	**CW4**	**CG**
Wax Conc. (% w/w)	**2.5**	**5**	**7.5**	**10**	**15**
Bulk density (g/cm^3)	0.48 ± 0.15	0.48 ± 0.12	0.47 ± 0.21	0.49 ± 0.23	0.30 ± 0.02
Tapped density (g/cm^3)	0.58 ± 0.20	0.59 ± 0.02	0.54 ± 0.01	0.55 ± 0.04	0.52 ± 0.03
Hausner's ratio	1.23 ± 0.05	1.22±0.05	1.14±0.05	1.12±0.05	1.11±0.05
Carr index (%)	19.1 ± 0.12	18.6±0.12	12.9±0.12	10.9±0.12	36.2 ± 1.20
Angle of repose (°)	27.20 ± 1.2	26.20 ± 1.1	25.40 ± 1.2	30.90 ±0.1	14.5 ± 0.12
Flow rate (g/sec)	1.14 ± 0.05	1.12 ± 0.12	1.15 ± 0.12	1.25 ±0.05	1.43±0.05
Entrapment efficiency (%)	70.0 ± 0.23	70.0 ± 0.42	70.0 ± 0.02	70.2 ± 0.02	99.0 ± 0.02

± Standard Deviation

Compatibility studies

DSC analysis

Thermograms from the DSC compatibility analysis are shown in Figure 1. Pure ibuprofen powder thermogram showed a sharp endothermic spike corresponding to 76 °C on the temperature scale which is the melting point of ibuprofen. The sharp spike is also an indication of its crystallinity and purity. The thermogram of the granules containing 10 %w/w of the fat showed the characteristic spike of pure ibuprofen. This observation suggests no interaction between the drug and the fat.

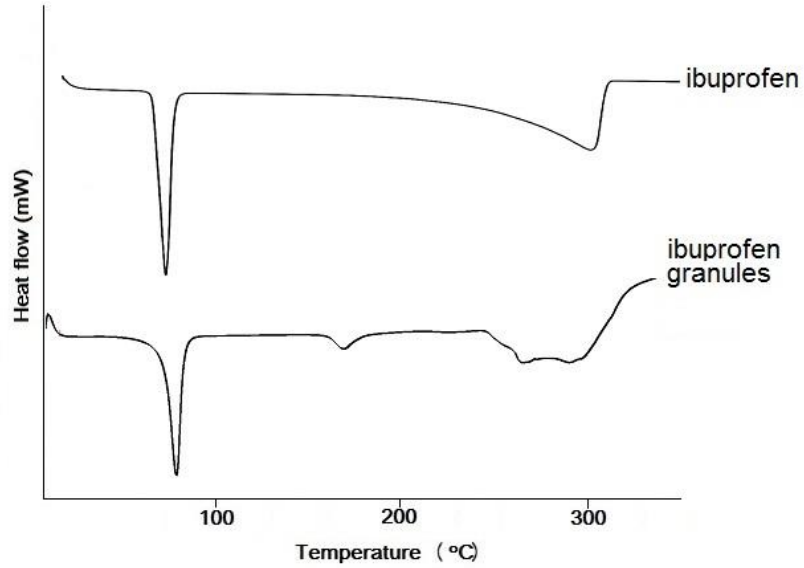

Figure 1: DSC thermograms of pure ibuprofen powder and the granules prepared with 10 %w/w of the SSD fat

FTIR

FTIR spectrum of pure ibuprofen exhibited characteristic absorption bands at 1228.58, 1422.61, 1717.58 and 2946.00 cm^{-1}. These bands observed for ibuprofen powder did not shift or disappear in the spectrum of the granules containing 10 %w/w of the fat. This suggests no chemical interaction or complex formation between ibuprofen and the fat during the mixing process.

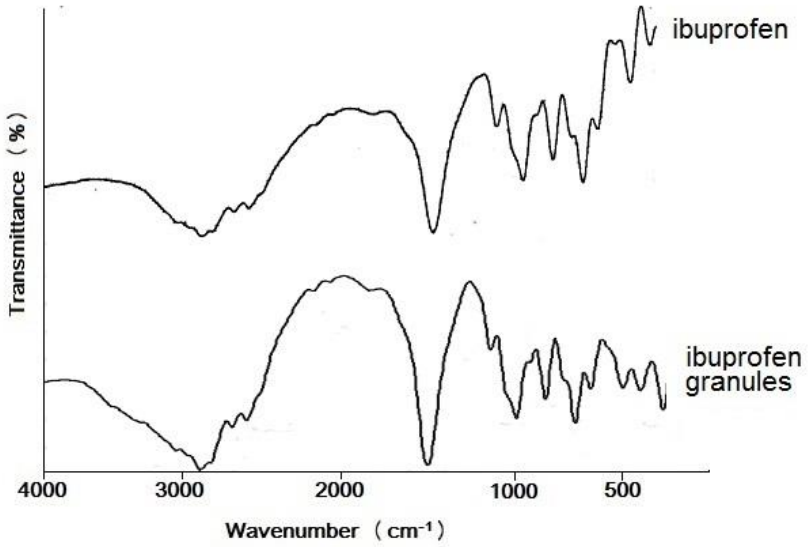

Figure 2: FTIR spectra of pure ibuprofen powder and the granules prepared with 10 %w/w of the SSD fat

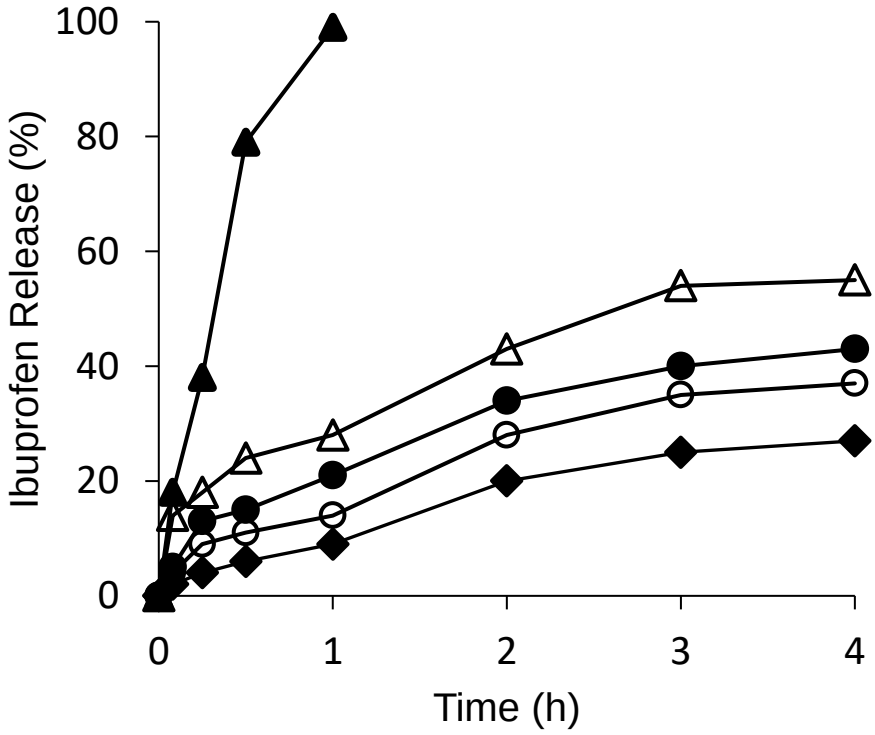

Figure 3a: Drug release profiles of ibuprofen granules prepared with varying concentrations of the SSD fat (2.5%w/w (△), 5.0%w/w (●), 7.5%w/w (○), 10.0%w/w (◆)) and maize starch mucilage (15 %w/w (▲))

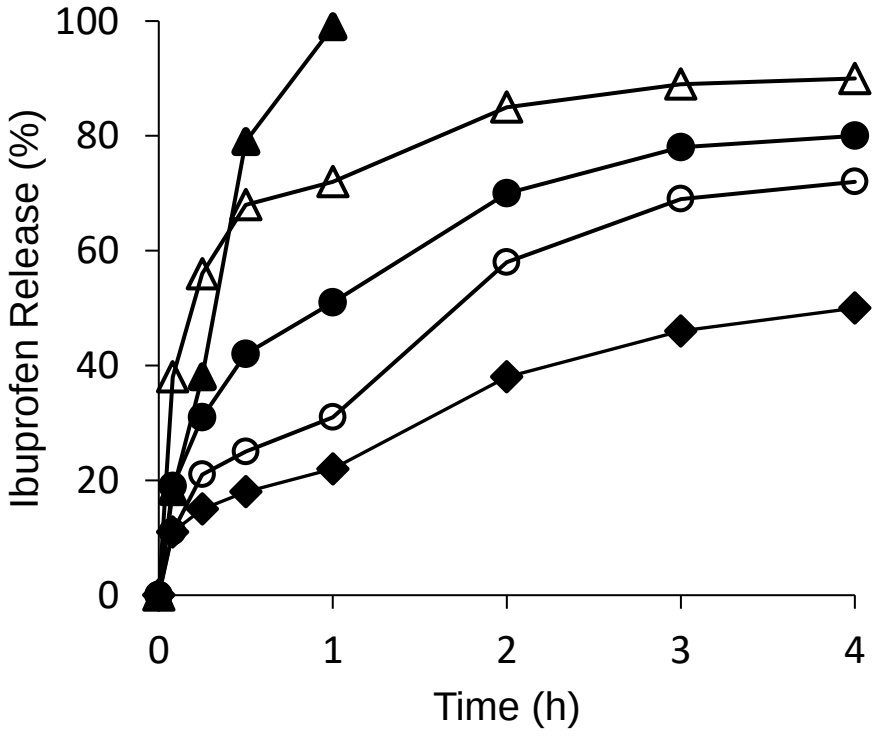

Figure 3b: Drug release profiles of ibuprofen granules prepared with varying concentrations of the carnauba wax (2.5%w/w (△), 5.0%w/w (●), 7.5%w/w (○), 10.0%w/w (◆)) and maize starch mucilage (15 %w/w (▲))

Dissolution profile

The release profiles of the different batches of the formulated ibuprofen granules are presented in Figures 3a and b. Generally, the drug release pattern showed decrease in drug release with increase in the concentrations of the fat or wax. The granules exhibited an initial burst release of drug in the first 5 minutes followed by drug release retardation with the batches of granules formulated with the fat showing more drug release retardation. BatchSD4 granules containing 10.0 %w/w of the fat exhibited the highest ibuprofen release retardation with a maximum percentage drug release of 27 % within 4 h and then followed by batches SD3 (7.5 %w/w) and SD2(5.0 %w/w) with percentage drug release of 37 and 43 %, respectively.

The highest drug release retardation from the carnauba wax batches of granules was achieved by the CW4 granules containing 10.0 %w/w of the wax with 50 % drug release within the 4 h of dissolution profiling. The conventional granules showed a drug release of 98.5 % in 1.0 h indicating rapid dissolution of drug from the surface of the granules.

The results of the release mechanism and kinetics of the drug from the batches of granules are shown in Table 3.Their correlation coefficient (r^2) values indicates that drug release was most in line with the Korsmeyer-Peppas model with $r^2 \geq 0.95$ and their release exponent (n) > 0.89, indicates that drug diffusion from the granules was Super Case-II diffusion mediated.

Table 3: Correlation coefficient (R^2) of the dissolution studies

Batches	Correlation coefficient (R^2)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas (n)
SD1	0.9230	0.9396	0.9813	0.9718 (1.51)
SD2	0.9408	0.9447	0.9902	0.9788 (1.34)
SD3	0.9415	0.9591	0.9777	0.9797 (1.23)
SD4	0.9587	0.9674	0.9656	0.9874 (1.03)
CW1	0.5820	0.8553	0.8088	0.9550 (1.85)
CW2	0.8116	0.9368	0.9645	0.9916 (1.71)
CW3	0.9163	0.9672	0.9807	0.9778 (1.57)
CW4	0.8889	0.9696	0.9844	0.9578 (1.43)
CG	0.9141	0.9636	0.9629	0.9759 (2.04)

4. DISCUSSION

A comparative evaluation of the sustained drug release ability of *Sus scrofa domesticus* fat and carnauba wax in ibuprofen matrix granule formulations has been investigated. The formulated granules of the fat and wax were found to differ in their flowability with the wax granules being superior. The low melting point of the fat has been implicated in the formation of cohesive granules with the particles sticking to each other and may have been responsible for the poor flowability of the granules prepared with the SSD fat (Uzochukwu *et al*., 2020). Again, the decrease in flowability with increase in the fat and wax would suggests a decrease in the porosity of the granules resulting from increased cohesiveness and densification of the particles with increasing amounts of the SSD fat or carnauba wax (Eichie *et al*., 2010,Arhewoh *et al*., 2015).

Additionally, the granules prepared with the fat also exhibited low drug loading capacity. It has been proposed that the high viscosity of the melted fat may play a role in hindering easy spread of the fat over drug powder particles (Uzochukwu *et al*., 2020), as similar low drug loading capacity values have be obtained with goat fat and where it was also observed that the loading capacity of the fat increases with the amounts of drug mixed with the fat (Ogbonna *et al*., 2015).

The encapsulated granules of both the fat and wax showed variable release pattern from their dissolution profiles. The initial burst of release seen within the first 5 min from all the formulations can be traced to the drug particles adhering to the granule surfaces. Theses adhering drug particles will immediately go into solution first when the granules come in contact with dissolution fluid before diffusion of drug from the core of the granules starts. Also, the diffusion of the drug from the core of the granule was dependent on the concentration of the fat or wax as less drugs was released with increased concentration. This observed decrease in drug release from the granules with increase in the concentrations of the fat or wax have been suggested by other studies as resulting from the increased tortuosity and reduced porosity of the granule particles leading to low water permeability which then acts as a rate controlling factor in retarding the release of drug from the granule system. Coupled with the low water permeability, the hydrophobic nature of the SSD fat and carnauba wax used in the formulation further compound the easy wetting of these granules, reducing the number of diffusion channels of the drug from the granules core and consequentially, reducing drug dissolution (Collett and Moreton, 2002, Tiwari *et al*., 2003, Abdelkader *et al*., 2008, Bruschi, 2015). The fat and wax used in the study

have been confirmed as hydrophobic in nature, hence they would impair rapid influx of fluid into the core of the granules and thereby contributing to the drug release retardation. Furthermore, another contributory factor to drug release retardation has been attributed to an increase in the diffusion path length of the drug with a corresponding increase in the fat or wax concentration in the granules leading to a retardation of drug release into the dissolution fluid or medium (Shah *et al.,* 2015).

5. CONCLUSION

Ibuprofen matrix granules was successfully formulated using *Sus scrofa domesticus* fat as a release retardant. Their granules were superior and compared favourably with carnauba wax in drug release retardation at all test concentrations. Hence *Sus scrofa domesticus* fat has a potential for sustaining drug release and it may find applications in sustained or controlled formulation of drugs with short biologic half-life where reduced frequency of dosing is desired.

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Authors' Contribution

FEE designed the study, COU performed the laboratory experiments while SOE prepared the manuscript for publication.

Competing Interest

There are no conflicts of interest in the study.

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Peer-review:

External peer-review was done through double-blind method.

Data and materials availability:

All data associated with this study are present in the paper.

Conference

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